Infrainguinal angioplasty with drug-eluting stents and balloons

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Objective: **The objective of this study was to provide a systematic review and meta-analysis of outcomes of infrainguinal angioplasty with drug-eluting stent (DES) or balloon (DEB).**
Methods: **The EMBASE, MEDLINE, and Cochrane databases and the Current Controlled Trials register were systematically interrogated for articles reporting results of infrainguinal angioplasty with DESs or DEBs. Clinical and angiographic end points were included.**
Results: **The review included 26 studies that reported on 2407 limbs; 11 were prospective randomized controlled trials. Infrapopliteal angioplasty with DEB was reported in 109 limbs (claudication, 19; critical limb ischemia [CLI], 90) (limb salvage in CLI, 95.6%; target lesion revascularization [TLR], 17.3%; mortality, 16%; mean follow-up, 12.3 months). Infrapopliteal angioplasty with DES was reported in 882 limbs (claudication, 160; CLI, 590; unclear severity, 132) (limb salvage in CLI, 97.4%, TLR, 10.8%; mortality, 17%; mean follow-up, 22.9 months). Femoropopliteal angioplasty with DES was reported in 1174 limbs (claudication, 301; CLI, 58; unclear severity, 815) (limb salvage in CLI, 89.6%; TLR, 17.3%; mortality, 3%; mean follow-up, 10.6 months). Femoropopliteal angioplasty with DEB was reported in 242 limbs (claudication, 182; CLI, 12; unclear severity, 48) (TLR, 10.6%; mortality, 2%; mean follow-up, 11 months). Meta-analysis of studies comparing DEB with standard balloon angioplasty demonstrated a result in favor of DEBs for preventing binary primary restenosis (odds ratio [OR], 0.27; $P = .005$) and TLR (OR, 0.17; $P = .001$). The meta-analysis comparing DESs with bare-metal stents demonstrated a result in favor of DES with regard to preventing TLR (OR, 0.15; $P = .001$) and binary primary restenosis (OR, 0.23; $P = .001$). Drug-eluting technology did not prevent more deaths or amputations.**
Conclusions: **Early angiographic data suggest that drug-eluting devices prevent restenosis in the short term, but there is as yet no evidence of an increase in limb salvage rates or a reduction in mortality. Further large randomized controlled trials with a focus on clinical outcomes and longer follow-up are needed. (J Vasc Surg 2014;59:1721-36.)**

Endovascular revascularization by balloon angioplasty is widely used in everyday clinical practice for the treatment of critical limb ischemia (CLI) due to infrainguinal atherosclerotic disease.[1] The BASIL (Bypass vs Angioplasty in Severe Ischaemia of the Leg) study compared percutaneous angioplasty with surgical bypass for treatment of severe lower limb ischemia in patients considered suitable for either approach.[2] After 2 years, both approaches achieved therapeutic equipoise with regard to amputation and survival. However, the major limitation of balloon angioplasty remains its durability, especially in treatment of below-the-knee lesions. A meta-analysis has demonstrated a 1-year primary patency of only 58% after crural angioplasty.[3]

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In an attempt to improve the durability of endovascular therapy, bare-metal stents (BMSs) have been developed but have been complicated by significant rates of stent thrombosis and neointimal hyperplasia. These problems have prompted the introduction of drug-eluting endovascular technology, initially developed for the coronary circulation. These technologies are designed to deliver antiproliferative drugs to the local vessel wall in an attempt to reduce restenosis.

Drug-eluting stents (DESs) were initially and subsequently widely used for coronary artery lesions.[4] The initial enthusiasm with DESs has been tempered by their drawbacks, including late stent thrombosis, need for prolonged dual antiplatelet therapy, and persistent restenosis.[5] The aim of this review was to collect all current published evidence regarding the role of angioplasty with use of drug-eluting balloons (DEBs) and DESs for infrainguinal arterial disease.

METHODS

A systematic review was performed by use of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[6]

Search strategy. A literature search was undertaken to identify all published English-language studies reporting results of infrainguinal angioplasty with DEBs and DESs. The EMBASE, MEDLINE, and Cochrane databases for

Table I. Assessment of methodologic quality and risk of bias in controlled studies

Study	*Adequate sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data addressed*	*Free of selective reporting*	*Free of other bias*
Duda[25]	?	?	− Angiographic outcomes + Clinical outcomes	−	−	−
Duda[26]	?	?	− Angiographic outcomes ? Clinical outcomes	−	−	−
Scheinert[13]	NA	NA	+	−	−	−
Bosiers[21]	?	?	−	+	−	−
Dake[28]	−	−	+	+	−	−
Rastan[20]	−	?	+	+	−	−
Scheinert[22]	−	?	+	+	−	−
Tepe[9]	−	?	+	−	−	−
Tepe[33]	?	?	+	+	−	−
Werk[10]	?	?	+	−	−	−
Falkowski[31]	−	?	+	−	−	−
Siabilis[32]	NA	NA	+	−	−	−
Werk[30]	−	−	−	−	−	−

+, High risk of bias; ?, unclear risk of bias; −, low risk of bias; *NA*, not applicable.

the period of 1950 to January 2013 and the Current Controlled Trials register were searched. Key words entered in this search were "drug-eluting stent" or "drug-eluting balloon," "femoropopliteal arteries," "below-the-knee arteries," and "angioplasty," with the Boolean operator odds ratio (OR). The reference lists of the articles obtained were reviewed for pertinent citations. Articles were excluded if they assessed the use of adjunctive procedures (laser, ultraviolet, or cryotherapy angioplasty) or pooled results, preventing analysis by segment of vessel treated. Studies were not excluded on the basis of disease severity.

When studies contained duplicate data, the paper with the most up-to-date or best documented material was used for analysis.

Data extraction. Data were extracted by two authors (L.C., B.O.). Studies were separated into four groups for the purpose of analysis:

Patients treated for infrapopliteal lesions with DEB angioplasty

Patients treated for femoropopliteal lesions with DEB angioplasty

Patients treated for infrapopliteal lesions with DESs

Patients treated for femoropopliteal lesions with DESs Four groups were used for the meta-analysis:

Studies comparing DES with BMS (pooled femoropopliteal and infrapopliteal)

Studies comparing DES with BMS (femoropopliteal)

Studies comparing DES with BMS (infrapopliteal)

Studies comparing DEB with standard percutaneous angioplasty (SPTA) (femoropopliteal)

Studies were assessed for methodologic quality and risk of bias by the guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions.*[7] These guidelines classify studies as at high, unclear, or low risk of bias with regard to adequacy of sequence generation, allocation concealment, blinding, accounting/addressing for incomplete data, freedom from selective reporting, and other biases. Data were extracted for study design; clinical outcomes—improvement in intermittent claudication, wound healing, major amputation (above ankle), limb salvage (defined as freedom from major amputation), amputation-free survival (defined as freedom from major amputation and death), and death; and angiographic outcomes—procedural technical success, binary primary restenosis, primary patency, late lumen loss (LLL), and target lesion revascularization (TLR). In studies comparing DEB with SPTA, additional intraoperative stenting of the target lesion after angioplasty was considered a technical failure.

Statistical analysis. Results quoted in the text refer to mean with range unless otherwise specified. The meta-analysis was performed with Review Manager version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). ORs and 95% confidence intervals (CIs) were calculated by the method of Mantel-Haenszel. Heterogeneity was assessed with the I^2 method. A fixed-effects model was used unless calculated I^2 was ≥25%.

RESULTS

Overall

We screened the title and abstract of 2241 potentially eligible publications. Of these, 2191 citations were excluded because they were not relevant to this study. Of the 50 studies further assessed for eligibility, 26 met the inclusion criteria, of which 11 were prospective randomized controlled trials and two were cohort studies with controls.[8-33] With two exceptions, all studies used the Rutherford-Baker classification of ischemia.[15,17] Only two studies applied both the guidelines of the Society for Vascular Surgery Ad Hoc Committee for reports dealing with extremity ischemia and the European consensus recommendations for reports of endovascular treatment for chronic lower limb ischemia.[21,29] Table I summarizes the results of the quality assessment of the included controlled

Table II. Study design and characteristics of patients and lesions of included studies of angioplasty with drug-eluting balloon (*DEB*)

First author	*Year*	*Study design*	*Patients, No.*	*Limbs treated, No.*	*CLI, %*	*Diabetes mellitus, %*	*Renal insufficiency, %*	*TASC*	*Lesion type, drug-eluting arm*	*Disease length, drug-eluting arm, mm*	*Lesion type, standard arm*	*Disease length, standard arm, mm*	*Follow-up, months*
Schmidt[8]	2011	Case series, DEB	104	109	82.6	71.2	46.2	No data	Not specified	176	NA	NA	12.3 ± 1
Tepe[9]	2008	Randomized controlled trial, DEB vs SPTA	102	102	—	38	—	No data	Mixed de novo, restenotic after SPTA, with stenting 8 (17%) and without stenting 10 (21%) and occlusions 13 (27%)	75	Mixed de novo, restenotic after SPTA, with stenting 6 (11%) and without stenting 10 (19%) and occlusions 14 (26%)	74	11.8
Werk[10]	2008	Randomized controlled trial, DEB vs SPTA	87	87	74	40	—	TASC II DEB: 14/45 A, 11/45 B, 16/45 C, 4/45 D SPTA: 21/42 A, 4/42 B, 10/42 C, 7/42 D	Mixed de novo, restenotic after SPTA, with stenting 14 (31%) and without stenting 2 (4%) and occlusions 6 (45%)	40	Mixed de novo, restenotic after SPTA, with stenting 8 (19%) and without stenting 10 (24%) and occlusions 4 (10%)	47	7.2
Micari[11]	2012	Case series, DEB	105	105	72.4	51	2	No data	109/114 de novo 4/114 restenotic 1/114 in-stent restenosis 34/114 total occlusions	176	NA	NA	11.7
Werk[30]	2012	Randomized controlled trial, DEB vs SPTA	85	91	4.4	35	0	No data	Mixed de novo, restenotic after SPTA, with stenting 7 (16%) and without stenting 7 (16%) and occlusions 10 (23%)	70	Mixed de novo, restenotic after SPTA, with stenting 6 (13%) and without stenting 2 (4%) and occlusions 18 (38%)	66	12

CLI, Critical limb ischemia; *NA,* not applicable; *SPTA,* standard percutaneous angioplasty; *TASC,* TransAtlantic Inter-Society Consensus.

studies. Several studies were judged to be of high or unclear risk of bias with regard to adequate sequence generation (5 of 11), allocation concealment (9 of 11), and blinding (11 of 13 for clinical outcomes, 6 of 12 for angiographic outcomes). The radiographic appearance of some DESs differs significantly from that of BMSs, and therefore blinding of several studies was uncertain. No study adequately prespecified the indication for reintervention for a lesion, and therefore the triggers for TLR have to be interpreted with caution.

Subgroups

Infrapopliteal angioplasty with DEB. Only one case series reported results of infrapopliteal angioplasty with DEBs (paclitaxel coated). The patient and lesion characteristics for this study are outlined in Table II[8]; 109 limbs with peripheral arterial disease (PAD: claudication, 17.4%; CLI, 82.6%) were treated. Lesion length was long (mean, 176 mm), and the majority of patients had "complete or functional" occlusion of all crural vessels (77.1%). The term *functional* was not defined. Outcomes are summarized in Table III. Procedural technical success, defined as a residual stenosis of the target lesion after angioplasty of less than 30%, was 95.5%. At 3 months, the primary patency was 72.6%. After a mean follow-up of 12.3 months, TLR was 17.3%, wound healing was 74.2%, limb salvage was achieved in 95.6% of the CLI patients, and mortality was 16%. The study was not designed to investigate primary or secondary patency out to this time interval.

Femoropopliteal angioplasty with DEB. Four studies reported results of femoropopliteal angioplasty with DEB (all paclitaxel coated), three of which were randomized trials comparing DEB with SPTA (Table II) (claudication, 182; CLI, 12; unclear severity, 48).[9-11,30] The 242 limbs with PAD were treated with DEBs. Procedural technical success was 91.2% (87.7%-100%). As the number of patients with CLI and in particular tissue loss was unclear (Tepe et al) or low (Rutherford class 4: 5 of 87, class 5: 0 of 87 [Werk et al]; class 4: 8 of 105, class 5: 0 of 105 [Micari et al]; class 4: 2 of 91, class 5: 2 of 91 [Werk et al]), these studies are underpowered to detect differences in limb salvage or death. After follow-up of 11.0 months (7.2-12 months), TLR rate was 7.7% (7.1%-10%) and mortality was 2% (range, 0%-4%). The trials demonstrated a

Table III. Angioplasty with drug-eluting balloon (*DEB*): Angiographic and clinical outcomes

First author	*Technical success*	*Primary patency, 3 months, %*	*Primary patency, 6 months, drug-eluting arm, %*	*Primary patency, 6 months, standard arm, %*	*Primary patency, 1 year, drug-eluting arm, %*	*TLR, drug eluting arm, %*	*TLR, standard arm, %*	*Limb salvage rate, drug-eluting arm, %*
Schmidt[8]	95.5	72.6	—	NA	—	17.3	NA	95.6
Tepe[9]	91.7		83	56	—	10	48	96
Werk[10]	91.1		94	94	—	7	33	100
Micari[11]	87.7		—	—	83.7	7.6	NA	No data
Werk[30]	100		91	68		7.1	27.9	100

ABPI, Ankle-brachial pressure index; *CLI,* critical limb ischemia; *f/u,* follow-up; *IC,* intermittent claudication; *PSVR,* peak systolic velocity ratio; *SPTA,* standard percutaneous angioplasty; *TLR,* target lesion revascularization.

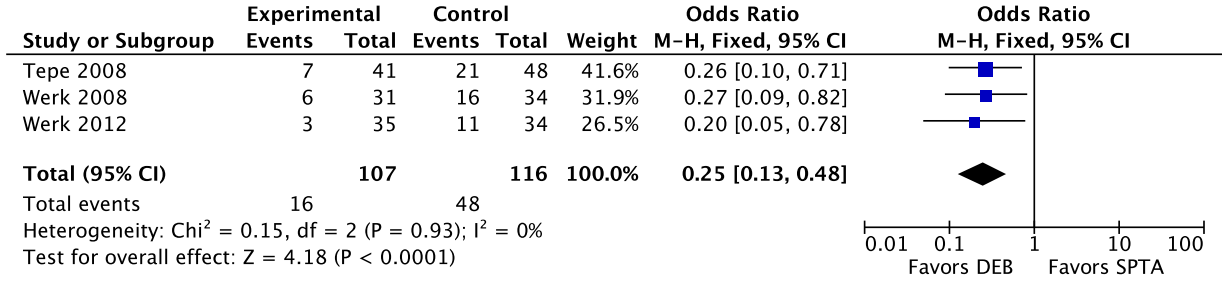

Fig 1. Comparison between drug-eluting balloon (*DEB*) and standard percutaneous balloon angioplasty (*SPTA*) in the femoropopliteal segment for binary restenosis rates. Forest plot of pooled results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

statistically significant reduction in the rate of TLR (Table III). Tepe et al and Werk et al (2012) clearly described the use of multiple DEBs for longer lesions, but lesions requiring further dilation because of residual stenosis >30% were treated with SPTA or BMSs. The study of Werk et al (2008) was unclear about the type of balloon used in lesions requiring further dilation.

Meta-analysis of DEB studies. The pooled result of the three controlled studies comparing DEBs with SPTA (all in the femoropopliteal segment) demonstrated a statistically significant result in favor of DEB for binary primary restenosis (≥50% of the reference vessel segment) (Fig 1) and TLR (Fig 2).[9,10,30] It was not possible to pool the results for other angiographic outcomes (Tepe reported LLL and standard deviation, Werk [2008] reported LLL and interquartile range, Werk [2012] reported LLL and 95% CI) or clinical outcomes (Tepe reported change in mean Rutherford class, Werk [2008 and 2012] reported categorical changes from baseline, Tepe [2008] reported ankle-brachial pressure index and standard deviation, Werk reported ankle-brachial pressure index and interquartile range). The event rate was too low to perform a

Table III. Continued.

Limb salvage rate, standard arm, %	*Rutherford class, drug-eluting arm*	*Rutherford class, standard arm*	*Change in Rutherford class at follow-up*	*Wound healing, %*	*Amputation-free survival, IC and CLI*	*Physiologic data*
NA	3: 19/109 4: 19/109 5: 70/109 6: 1/109	—	Clinical improvement in 91.2% of limbs At follow-up: class 0: 61/91; class 1: 6/91; class 2: 5/91; class 3: 2/91; class 4: 7/91; class 5: 10/91; class 6: 0/91	74.20	85/104	No data
100	Mean, 3.4	Mean, 3.1	Mean DEB, 1.2; STPA, 1.6	No data	No data	ABPI pre: 0.5 DEB, 0.5 SPTA ABPI f/u: 0.8 DEB, 0.8 SPTA
98	1: 2/45 2: 10/45 3: 31/45 4: 2/45	1: 1/31 2: 7/42 3: 31/42 4: 3/42	Related to baseline: DEB worsened, 0/45; equal, 8/45; improved, 26/45; missing, 11/45	No data	1/45 DEB; 1/42 SPTA	ABPI pre: 0.8 DEB, 0.9 SPTA ABPI f/u: 0.8 DEB, 0.8 SPTA
	1: 1/105 2: 28/105 3: 8/105 4: 8/105	NA	0: 60/92 1: 17/92 3: 13/92 4: 2/92 (derived from graphic data)	NA	89/92	ABPI pre: 0.56 ABPI f/u: 0.86 PSVR pre: 3.1 PSVR f/u: 1.2.
100	2: 4/44 3: 38/44 4: 0/44 5: 2/44	2: 6/47 3: 39/47 4: 2/47 5: 0/47	Related to baseline: DEB worsened, 0/44; equal, 8/44; improved, 32/44; missing, 4/44	No data	42/42 DEB; 40/43 SPTA	No data

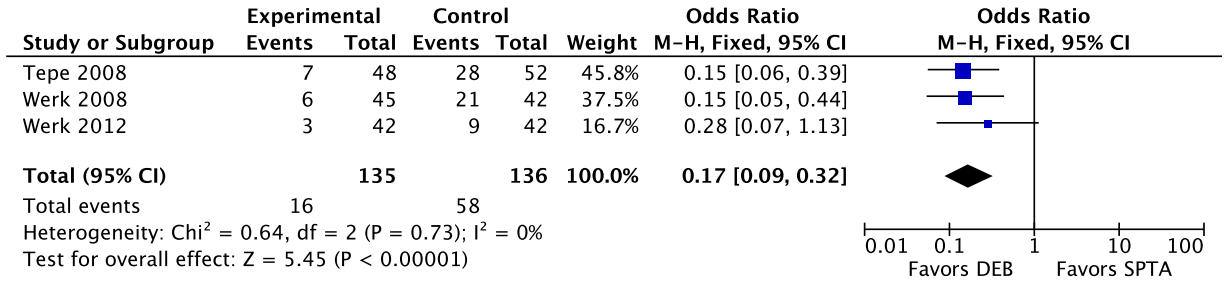

Fig 2. Comparison between drug-eluting balloon (*DEB*) and standard balloon percutaneous angioplasty (*SPTA*) in the femoropopliteal segment angioplasty for target lesion revascularization (TLR). Forest plot of pooled results from comparative studies. *CI,* Confidence interval, *M-H,* Mantel-Haenszel.

meaningful meta-analysis for the amputation and death outcomes (amputation: DEB 2 of 137, SPTA 1 of 135; death: DEB 2 of 137, SPTA 5 of 135).

Infrapopliteal angioplasty with DES. Fifteen studies reported the results of infrapopliteal angioplasty with DESs (Table IV); 882 limbs were treated with DESs (claudication,160; CLI, 590; unclear severity, 132).[12-14,16-24,31-33] A variety of coatings were used for the DESs (nine studies used sirolimus; one, everolimus; three, sirolimus/paclitaxel; one, sirolimus/everolimus/paclitaxel; one, sirolimus/zotarolimus/everolimus). Technical success rates of 99.0% (90.7%-100%) were achieved. Mean follow-up was 22.9 months (6.5-47.5 months). TLR rate was 10.8% (0%-81.1%), limb salvage was achieved in 97.4% (78.8%-100%) of the CLI patients, and mortality was 17% (range, 0%-32%). Seven studies were comparative (vs either SPTA or BMS), of which five were randomized controlled trials. Tepe and Siabilis had longer clinical follow-up than the other comparative studies. Differences between DES, BMS, and SPTA in amputation-free survival were not observed by Tepe (amputation-free survival: DES 11 of 14, BMS 11 of 16, SPTA 11 of 14). Limb salvage and patient mortality

Table IV. Study design and characteristics of patients and lesions of included studies of angioplasty with drug-eluting stent (*DES*)

First author	*Year*	*Study*	*Patients, No.*	*Limbs treated, No.*	*CLI, %*	*Diabetes mellitus, %*	*Renal insufficiency, %*	*TASC*
Scheinert[12]	2006	Cohort with control, DES vs BMS	60	60	74.6	83.3	43.2	No data
Commeau[13]	2006	Case series, DES	30	30	86.6	36.6	No data	TASC I C
Bosiers[14]	2006	Case series, DES		18	100	87.3	43.2	No data
Feiring[15]	2007	Case series, DES	5	5	100	100	100	No data
Rosales[16]	2008	Case series, DES	24	24	100	83	41	No data
Grant[17]	2008	Case series, DES	10	10	90	50	—	No data
Feiring[18]	2010	Case series, DES	106	130	100	83.3	10	No data
Lookstein[19]	2011	Case series, DES	67	67	100	72	43	No data
Rastan[20]	2012	RCT, DES vs BMS	161	161	46.6	53.8	35.4	No data
Bosiers[21]	2012	RCT, DES vs BMS	140	140	100	60	30	No data
Scheinert[22]	2012	RCT, DES vs SPTA	200	200	Unclear	64.6	—	No data
Spiliopoulos[23]	2012	Case series, DES	39	41	100	61.6	5.1	No data
Werner[24]	2012	Case series, DES	158	158	43.7	65	—	No data
Duda[25]	2002	RCT, DES vs BMS	36	36	No data	50	No data	TASC I C
Duda[26]	2005	RCT, DES vs BMS	57	57	38.9	50	—	No data
Dake[27]	2011	Case series DES	787	787	No data	36.2	No data	TASC II 236/900 A 265/900 B 228/900 C 126/900 D 45/900 not assessed
Dake[28]	2011	RCT, DES vs BMS	474	474	9	49.2	10.2	No data
Lammer[29]	2011	Case series DES	104	104	17	39	No data	TASC II 44/106 A 48/106 B 14/106 C 0/106 D
Tepe[33]	2010	RCT, DES vs BMS and SPTA	44	44	100	65.9	No data	No data
Falkowski[31]	2009	RCT, DES vs BMS	50	50	36	40	No dialysis patients	No data
Siablis[32]	2009	Cohort with control, DES vs BMS	103	122	100	82	49	No data

BMS, Bare-metal stent; *CLI,* critical limb ischemia; *NA,* not applicable; *RCT,* randomized controlled trial; *SPTA,* standard percutaneous angioplasty; *TASC,* TransAtlantic Inter-Society Consensus.

were observed to be similar between DESs and BMSs by Siabilis (limb salvage: DES 80.3% vs BMS 82.0%, $P = .507$; and death: DES 29.3% vs BMS 32%, $P = .205$).[32,33] It was not possible to extract or to derive data on wound healing for these studies. Table V outlines outcomes for the published case series.

Femoropopliteal angioplasty with DES. Six studies reported results of femoropopliteal angioplasty with DES (Table IV) (claudication, 301; CLI, 58; unclear severity, 815).[15,25-29] A variety of coatings were used for the DESs (three studies used sirolimus; one, everolimus; two, paclitaxel). Three were randomized controlled trials comparing DESs with BMSs or SPTA; 1174 limbs with PAD were treated. Technical success was 92.7% (range, 95%-100%). Mean follow-up was 10.6 months (6-12 months). TLR was 10% (0%-20%), limb salvage was achieved in 89% of the CLI patients, and mortality was 3% (range, 0%-6%). (Table V). A statistically significant decrease in the rate of TLR was demonstrated in only the two more recent prospective randomized studies (Table V).

Meta-analysis of DES studies. The pooled results of the comparative studies of DES vs BMS demonstrated a statistically significant result in favor of DES with regard to binary primary restenosis (Fig 3), TLR (Fig 4), and LLL (Fig 5) but not amputation (Fig 6) or death (Fig 7). The observation persisted in subgroup analysis of the infrainguinal segment (Figs 8 to 12). Only the binary restenosis rate was improved by DES use in the femoropopliteal segment (Fig 13). The rates of LLL (OR, −0.22; 95% CI, −0.69 to 0.26; $P = .38$) and death

Table IV. Continued.

Lesion type, drug-eluting arm	*Disease length, drug-eluting arm, mm*	*Lesion type, standard arm*	*Disease length, standard arm, mm*	*Follow-up, months*
All de novo occlusions 6/30	≤30	All de novo occlusions 7/30	≤30	6.5 angiographic 9.6 clinical
All de novo	No data	NA	NA	7.7 ± 5.8
No data	No data	NA	NA	6
All de novo	No data	NA	NA	29 ± 8
No data	No data	NA	NA	9.5
No data	24.8	NA	NA	12.4 ± 6.5
No data	No data	NA	NA	27.4 ± 18.6
No data	49.7	NA	NA	20
All de novo No data on occlusions	31	All de novo No data on occlusions	31	33.9
All de novo occlusions 12/78	15.9	All de novo occlusions 13/76	18.9	12
Mixed de novo, restenotic 6/113 and occlusions 92/113	26.9	Mixed de novo, restenotic 2/115 and occlusions 87/115	26.8	12
All de novo	31.3	NA	NA	47.5 ± 14.8
Mixed de novo, restenotic 50 (31.6%) and occlusions 41 (31.6%)	≥80	NA	NA	31.16 ± 20.3
Mixed de novo, restenotic and occlusions (10/18)	82.9	Mixed de novo, restenotic and occlusions (11/18)	88.6	6
Mixed de novo, restenotic 3 (10%) and occlusions 22 (76%)	86.5	Mixed de novo, restenotic 1 (4%) and occlusions 16 (57%)	76.3	6
Mixed de novo, restenotic 219 (24.3%), occlusions 345 (38.3%), and in-stent stenosis 130 (14.4%)	99.5 431/900 >70 202/900 >150	NA	NA	12
All immediate procedural failure	≤140 (about 65)	All immediate procedural failure	≤140 (about 65)	12
Mixed de novo, restenotic (9.4%) and occlusions (45%)	9	NA	NA	12
Occlusion 28.6%	27	BMS: occlusion 37.5% SPTA: occlusion 28.6%	BMS: 35 SPTA: 31	6 angiographic 2-4 years clinical
No data	17	No data	18.2	6
All failed primary SPTA Occlusion 37/153	45	All failed primary SPTA Occlusion 27/77	45.18	36

(OR, 0.42; 95% CI, 0.06-2.97; $P = .39$) were not different between groups in the femoropopliteal segment. The TLR and amputation rates were not compared in the femoropopliteal segment because of the very low event rate for results to be meaningful (TLR: DES 0 of 47, BMS 0 of 46; amputation: DES 1 of 61, BMS 2 of 62). It was not possible to report the results for other clinical outcomes because of differences in the type or manner in which outcomes were reported (change in Rutherford class reported as numbers improving, groups before and after intervention, median or not provided; only two studies reported ankle-brachial pressure index data, and one reported transcutaneous partial pressures of oxygen). When we restricted our analysis to only randomized controlled trials (removing the two infrapopliteal cohort studies with controls), the overall pooled and infrapopliteal subgroup results were unchanged:

Pooled DES vs BMS—binary restenosis: OR, 0.16; 95% CI, 0.09-0.30; $P < .0001$; TLR: OR, 0.26; 95% CI, 0.14-0.48; $P < .0001$; amputation: OR, 0.31; 95% CI, 0.06-1.56; $P = .16$; death: OR, 1.02; 95% CI, 0.57-1.82; $P = .95$.

Infrapopliteal DES vs BMS—binary restenosis: OR, 0.12; 95% CI, 0.05-0.28; $P < .0001$; TLR: OR, 0.25; 95% CI, 0.13-0.47; $P < .0001$; amputation: OR, 0.31; 95% CI, 0.06-1.56; $P = .16$; death: OR, 1.02; 95% CI, 0.57-1.82; $P = .95$.

DISCUSSION

This systematic review and meta-analysis has demonstrated that DESs and DEBs have encouraging technical

Table V. Angioplasty with drug-eluting stent (*DES*): angiographic and clinical outcomes

First author	*Technical success*	*Patency, 6 months, drug-eluting arm, %*	*Patency, 6 months, standard arm, %*	*Patency, 1 year, drug-eluting arm, %*	*Patency, 1 year, standard arm, %*	*Patency, 2 years, drug-eluting arm, %*	*TLR, drug-eluting arm, %*	*TLR, standard arm, %*	*Limb salvage rate, drug-eluting arm, %*	*Limb salvage rate, standard arm, %*
Scheinert[12]	100	—	—	100	65	—	0	23.3	100	90
Commeau[13]	100	—	NA	97	NA	—	0	NA	100	NA
Bosiers[14]	100	—	—	—	—	—		0	94	NA
Feiring[15]	100	—	NA	100	NA	—	NA	0	100	NA
Rosales[16]	96	—	NA	89.4	NA	—	NA	0	84	NA
Grant[17]	100	—	NA	90	NA	—	NA	10	100	NA
Feiring[18]	90.7	—	NA	92.4	NA	—	NA	15	95	NA
Lookstein[19]	100	90		86		72		—	91.1	NA
Rastan[20]	No data	No data	No data	No data	No data	No data	9.2	12.9	97.4	87.1
Bosiers[21]	100	—	—	85	84	—	9	35	98.6	96.9
Scheinert[22]	95.5	—	—	77.6	57.1	—	10	16.6	86.2	80
Spiliopoulos[23]	100	—	NA	73.6	NA	42.7	8 at 1 year		At 1 year, 84.3	
Werner[24]	100	—	—	87	NA	85	0		At 1 year, 93.3 At 2 years, 78.8	NA
Duda[25]	100	100	58.9	—	—	0	0	0	100	100
Duda[26]	100	100	93	—	—	0	0	0	100	100
Dake[27]	97.6	—	—	86.2	NA	9.5	NA		No data	NA
Dake[28]	95	—	—	83.1	32.8	—	9.5	17.5	100	100
Lammer[29]	98	94	—	68	NA	—	30	NA	—	NA
Tepe[33]	100	91	33 (BMS), 25 (SPTA)	—	—	—	7	14 (BMS) 15 (SPTA)	93	86 (BMS) 84 (SPTA)
Falkowski[31]	100	16	19	—	—	—	12	14	100	100
Siablis[32]	96	—	—	—	—	3 years: DES 32.9, BMS 17.1	81.1	96.3		

ABPI, Ankle-brachial pressure index; *BMS,* bare-metal stent; *CLI,* critical limb ischemia; *f/u,* follow-up; *IC,* intermittent claudication; *NA,* not applicable; *TLR,* target lesion revascularization.

Table V. Continued.

Rutherford class, drug-eluting arm	*Rutherford class, standard arm*	*Change in Rutherford class at follow-up*	*Wound healing, %*	*Amputation-free survival, IC and CLI*	*Physiologic data*
3: 11/30 4: 8/30 5: 11/30	3: 10/30 4: 11/30 5: 9/30	Assisted improvement by 1 class, 22/30 DES and 18/30 BMS	No data	Not able to calculate	No data
3: 4/30 4: 16/30 5: 7/30 6: 3/30	NA	0: 19/28 1: 2/28 2: 6/28 5: 1/28	9/10	28/30	No data
4: 12/18 5: 4/18 6: 2/18	NA	95.7% < class 3	No data	94.1	No data
4: 2/5 5: 3/5	NA	5/5 < class 4	3/3	5/5	ABPI pre: 0.32 ABPI f/u: 0.58 Toe pressure pre: 21 mm Hg Toe pressure f/u: 46 mm Hg
24/24 > class 3	NA	No data	No data	20/24	No data
Fontaine class IIb: 1/10 III: 4/10 IV: 5/10	NA	No data	No data	10/10	No data
4: 45/118 5: 36/118 6: 37/118	NA	Improved at follow-up (healed/relief of rest pain), 104/111	68/74	68/118 (derived from graphic data)	No data
4: 14/67 5: 42/67 6: 11/67	NA	No data	No data	88	No data
3: 40/82 42/82 ≥ class 4	3: 46/79 33/79 ≥ class 4	0/44 worse by 1 class 7/44 no change DES 2/44 worse by 1 class 15/44 no change BMS	No data	Not able to calculate	No data
4: 37/74 5: 37/74	4: 26/66 5: 40/66	DES: class 0: 26/53; class 1: 6/53; class 2: 5/53; class 3: 4/53; class 4: 5/53; class 5: 5/53; class 6: 2/53 BMS: class 0: 20/45; class 1: 5/45; class 2: 6/45; class 3: 7/45; class 4: 0/45; class 5: 6/45; class 6: 1/45	No data	Not able to calculate	No data
Mean, 4.1	NA	Improvement in Rutherford class: DES 54/71 and SPTA 51/76	No data	Not able to calculate	No data
4: 29/41 5: 9/41 6: 3/4	NA	Not specified	No data	33/39	No data
3: 89/158 4: 19/158 5: 32/158 6: 18/158	NA	Sustained improvement by at least 1 Rutherford category in 59/77 claudicants and 54/59 patients with CLI	No data	63% claudicants and 41% CLI patients	No data
1-2: 7/18 3-4: 11/18	1-2: 12/18 3-4: 6/18	No numerical data regarding changes in Rutherford class	NA	100%	No data
0-2: 13/29 3-4: 16/29	0-2: 14/28 3-4: 14/28	DES: class 0: 23/24; class 1-2: 1/24 BMS: class 0: 18/26; class 1-2: 7/26; class 3-4: 1/26	NA	27/29 DES; 27/28 BMS	ABPI pre: 0.67 DES, 0.61 BMS ABPI f/u: 0.92 DES, 0.88 BMS
Median Rutherford class, 3	NA	Median, 0	No data	No data	ABPI pre: 0.6 ABPI f/u: 0.9
About 10% CLI	About 10% CLI	Not provided for subgroups of interest for meta-analysis	Not provided for subgroups of interest for meta-analysis	Not provided for subgroups of interest for meta-analysis	No data
2: 36/104 3: 52/104 4: 9/104 5: 9/104	—	Sustained benefit by at least 1 class in 83/104	No data	16/18 in CLI patients	ABPI pre: 0.64 ABPI f/u: 0.89
5-6: 14/14	5-6: 16/16 (BMS) 5-6: 14/14 (SPTA)	2- to 4-year follow-up: DES 9/11 < class 4 BMS 8/11 < class 4 SPTA 6/11 < class 4	2- to 4-year follow-up: DES 9/11 BMS 8/11 SPTA 6/11	2- to 4-year follow-up: DES 11/14 BMS 11/16 SPTA 11/14	Toe pressure before intervention and at 6 months: DES 18 to 25 mm Hg BMS 20 to 40 mm Hg SPTA 15 to 30 mm Hg
3: 16/25 4: 6/25 5: 3/25	3: 18/25 4: 4/25 5: 3/25	6-month data not provided	No data	100	ABPI pre: DES 0.5, BMS 0.5 ABPI f/u: DES 0.7, BMS 0.6
4: 26/62 5: 26/62 6: 10/62	4: 15/41 5: 16/41 6: 10/41	No data	No data	Not able to calculate	No data

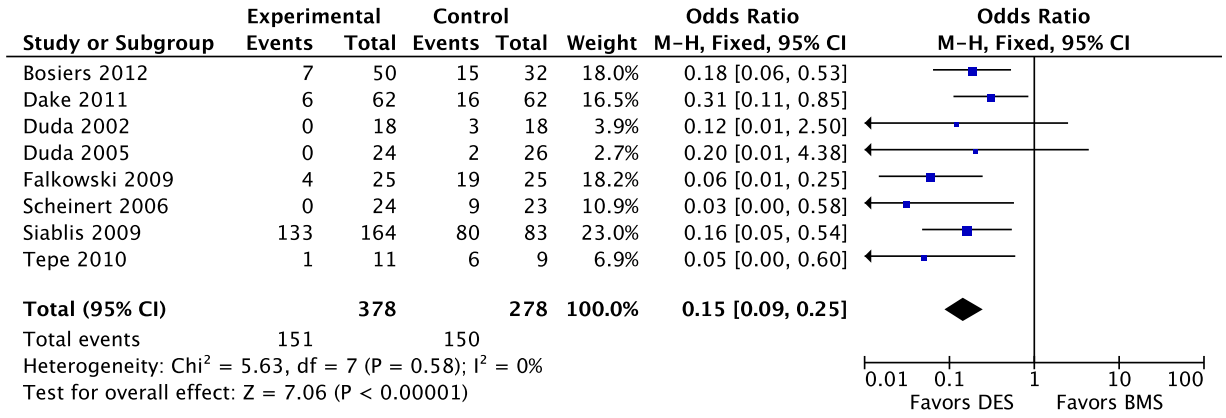

Fig 3. Pooled infrainguinal comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty for binary restenosis rates. Forest plot of pooled results from comparative studies. For Dake 2011, only the subgroup that randomized patients to either DES or BMS after failed standard balloon percutaneous angioplasty (SPTA) was used in the analysis. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

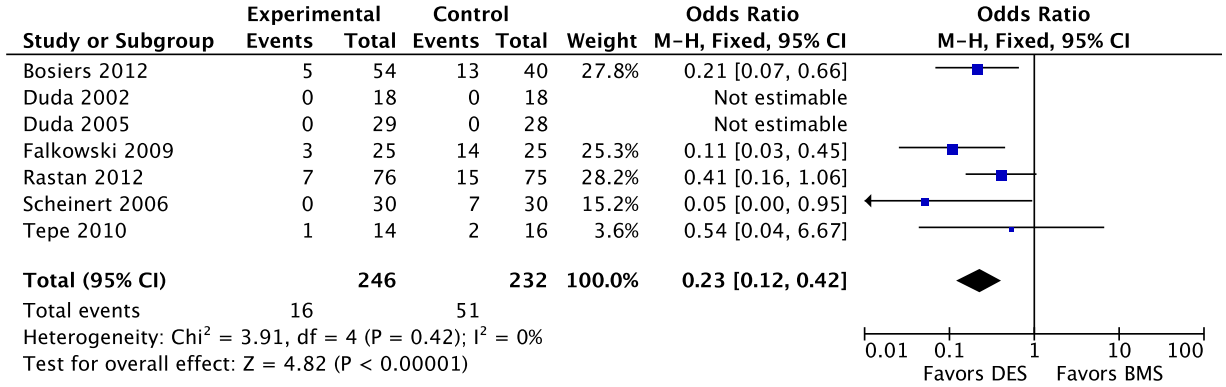

Fig 4. Pooled infrainguinal comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty for target lesion revascularization (TLR). Forest plot of pooled results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

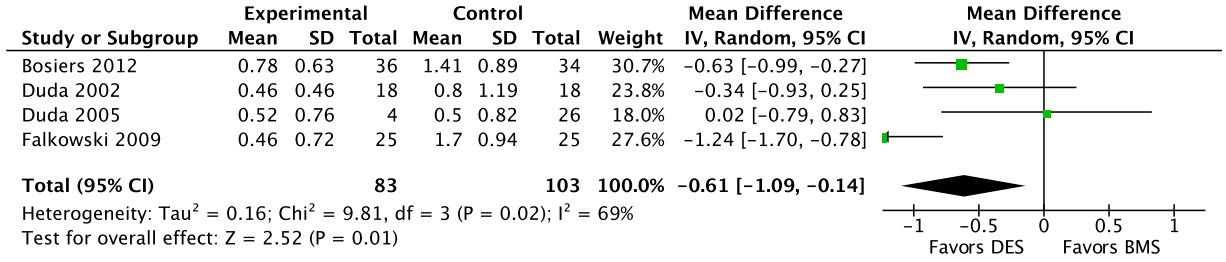

Fig 5. Pooled infrainguinal comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty for late lumen loss (LLL, mm). Forest plot of pooled results from comparative studies. *CI,* Confidence interval; *IV,* inverse variance; *SD,* standard deviation.

and radiologic success rates in the short to medium term. However, longer term follow-up and better designed randomized trials (allocation concealment/blinding) with more patient-centered and focused outcomes (including amputation-free survival) in patients with CLI are really required before the technology can be recommended for everyday clinical practice. Similar initial excitement about other endovascular technologies for PAD, such as laser atherectomy, has failed to transfer to routine mainstream practice because of lack of evidence.[34]

Drug-eluting devices for treatment of PAD first used in the femoropopliteal segment initially failed to demonstrate

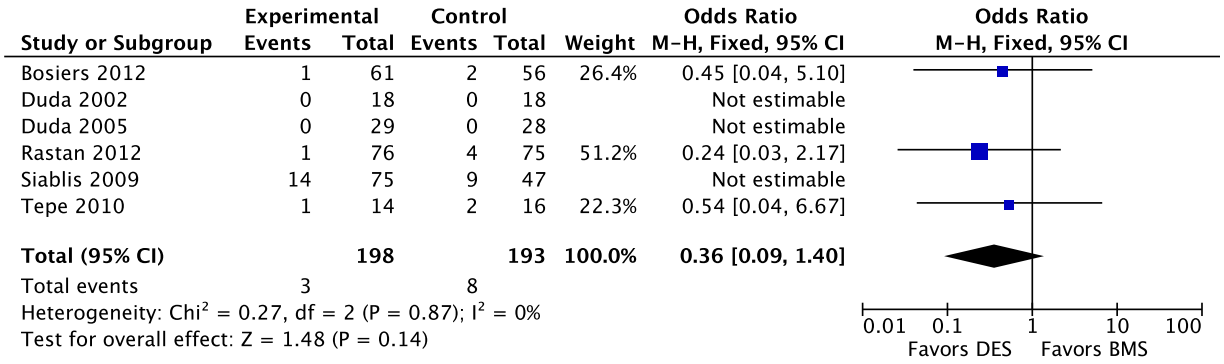

Fig 6. Pooled infrainguinal comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty for amputation. Forest plot of pooled results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

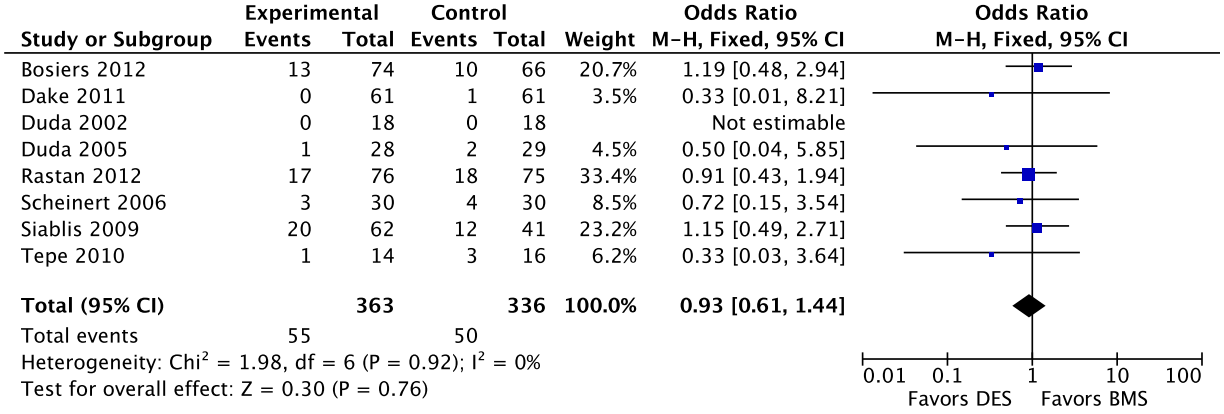

Fig 7. Pooled infrainguinal comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty for death. Forest plot of pooled results from comparative studies. For Dake 2011, only the subgroup that randomized patients to either DES or BMS after failed standard balloon percutaneous angioplasty (SPTA) was used in the analysis. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

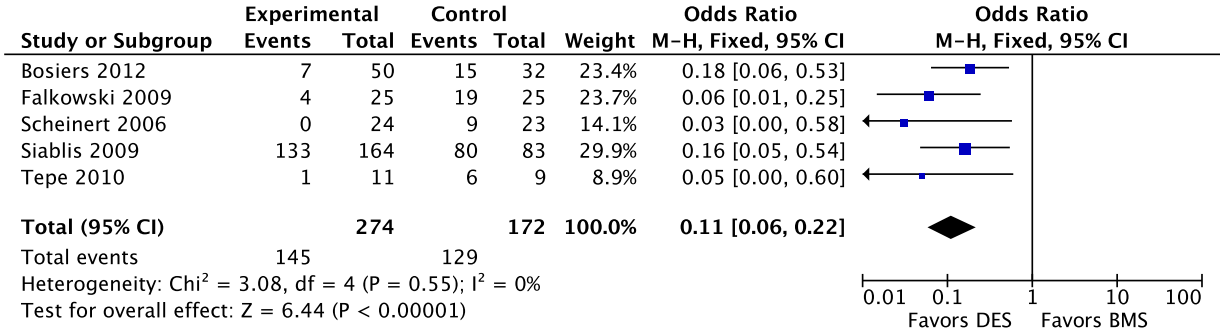

Fig 8. Comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty in the infrapopliteal segment for binary restenosis rates. Forest plot of results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

any substantial benefit even with binary restenosis rates.[25,26] One potential explanation for these initial poor results may be inadequate drug delivery (90 μg sirolimus/cm^2 stent area) and that the stent platform was prone to fracture (18% at 6 months). Recently presented 3-year TLR rates favor DES over BMS angioplasty (83% vs 70.2%, respectively).[28] The prevalence of stent fracture rates at 12 months was only 0.4%. The Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) study was a prospectively collected case series describing

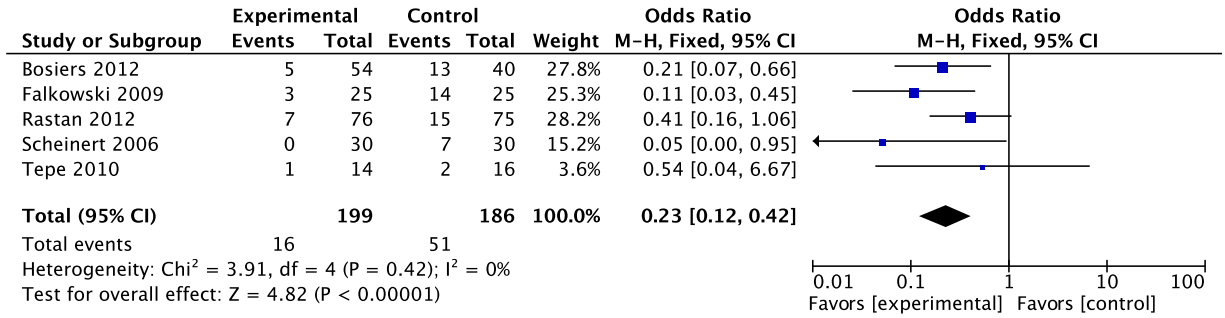

Fig 9. Comparison between drug-eluting stent (DES) and bare-metal stent (BMS) angioplasty in the infrapopliteal segment for target lesion revascularization (TLR). Forest plot of results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

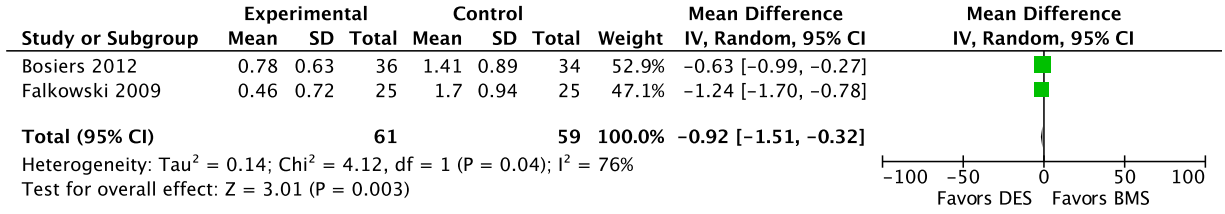

Fig 10. Comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty in the infrapopliteal segment for late lumen loss (LLL, mm). Forest plot of results from comparative studies. *CI,* Confidence interval; *IV,* inverse variance; *SD,* standard deviation.

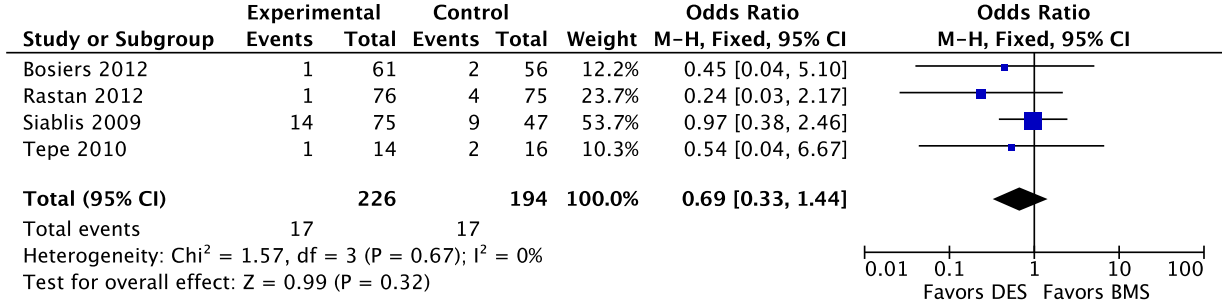

Fig 11. Comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty in the infrapopliteal segment for amputation. Forest plot of results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

the use of a novel everolimus-eluting stent.[29] The results are noteworthy, given that the initial favorable primary patency rate of 94% at 6 months was not sustained at 12 months (68%). It is difficult to conclude, therefore, that the everolimus-eluting peripheral DES represents a significant advance in currently available interventional technology. The lack of efficacy cannot be explained by the stent platform (no stent fracture reported), but it may still be explained by either inadequate drug delivery or the coating used.

The management of patients with infrapopliteal disease is historically challenging. Diabetes and renal failure are more common in these patients, and consequently angiographically difficult long calcified lesions are more frequent. A recent systematic review of balloon angioplasty for below-the-knee arteries demonstrated a 1-year primary patency rate between 33% and 37%.[35] Two randomized controlled trials failed to show the superiority of primary infrapopliteal stenting over balloon angioplasty alone.[36,37] Despite the introduction of drug-eluting devices with a great deal of expectation, this review highlights that the evidence for clinical as opposed to angiographic superiority is at present lacking. There are currently three randomized trials under way to evaluate the benefits of DEBs in the infrapopliteal segment: DEBATE-BTK (primary outcome measure: binary restenosis; interim results: 27% DEB, 56% SPTA; study completion expected November 2013); IN.PACT DEEP (primary outcome measures: LLL, TLR,

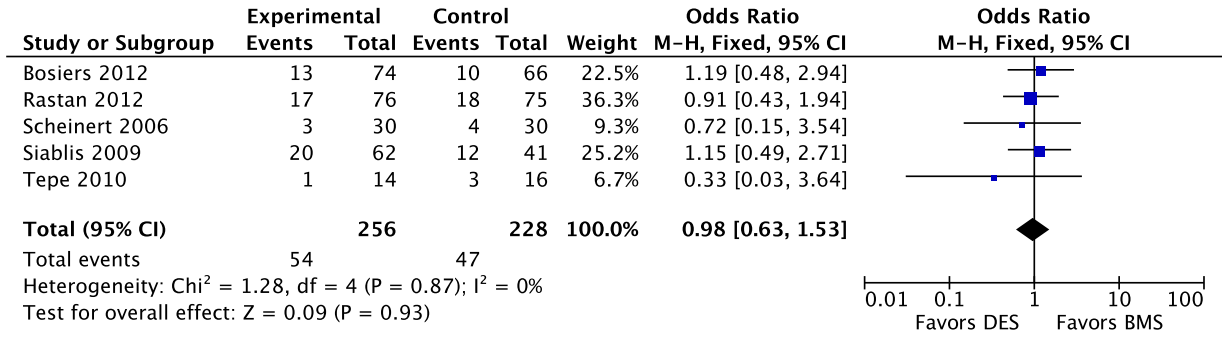

Fig 12. Pooled infrainguinal comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty in the infrapopliteal segment for death. Forest plot of results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

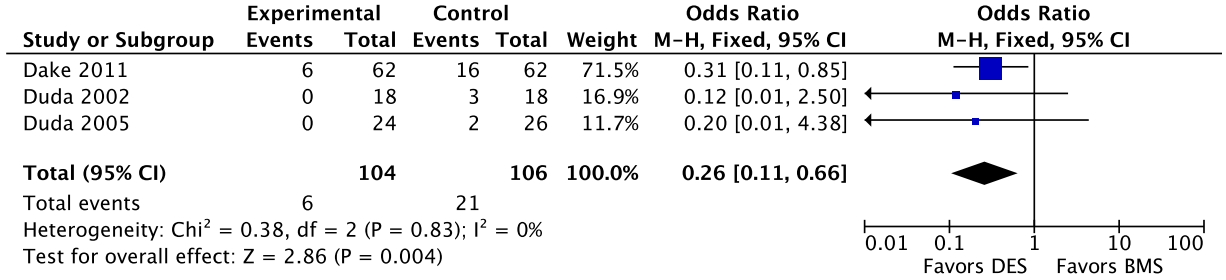

Fig 13. Comparison between drug-eluting stent (*DES*) and bare-metal stent (*BMS*) angioplasty in the femoropopliteal segment for binary restenosis rates. Forest plot of results from comparative studies. *CI,* Confidence interval; *M-H,* Mantel-Haenszel.

and composite all-cause death/major amputation/TLR; expected primary completion August 2013; expected study completion August 2017); and EURO CANAL (outcome measures: LLL, amputation-free survival, TLR; temporarily stopped recruiting). Preliminary results from IN.PACT demonstrate a primary restenosis rate >50% after 3 months in 69% of patients treated with SPTA and only 31% of patients treated with DEB.[38] Clinical improvement is evident in 36 of 48 patients (75%) in the DEB group. Of these trials, only EURO CANAL is looking at amputation-free survival as a primary outcome. This is unfortunate as this is the most clinically relevant and therefore useful outcome. The emphasis in the other trials is still on radiologic primary outcomes, and therefore they are unlikely to significantly add to our understanding of the effectiveness, or not, of drug-eluting technology.

The use of DESs for infrapopliteal angioplasty is better reported. The five randomized controlled trials all demonstrate a statistically significant decrease in the rate of TLR. However, to date, only one prospective randomized study has evaluated the use of DESs for long (>7 cm) infrapopliteal lesions and demonstrated significantly better primary patency rate at 13.1 months.[9] The two comparative studies with the longest follow-up did not demonstrate a reduction in limb loss or survival with DESs.[32,33]

The early enthusiasm for use of drug-eluting devices in infrainguinal vessels was tempered by the results of several small negative studies.[26,29] However, new trials, using modified stent platforms, DEBs, or variations of type and dosage of drug, suggest that drug-eluting technology may reduce restenosis rates. This meta-analysis demonstrated a statistically significant impact in favor of DEB to STPA for binary primary restenosis and TLR and in favor of DES to BMS in regard to TLR, binary primary restenosis rate, and LLL. However, it was not possible to pool the results for other angiographic or clinical outcomes because of differences in the type of outcomes or the manner in which they were reported. Many of these studies have drawbacks (short mean lesion length, short-term follow-up). Most studies presented pooled data from patients with intermittent claudication, rest pain, and tissue loss as well as from patients with and without diabetes. These represent significantly different prognostic groups, and therefore healthy interpretation of results is challenging. Many questions about the use of drug-eluting devices for PAD remain to be answered. It will be important for future studies to be designed and powered to address the more fundamental question of whether drug-eluting technology improves clinical outcomes, such as amputation-free survival. The potential benefit of drug-eluting devices for certain lesions and patient subgroups, such as in-stent restenosis and diabetic patients, will need to be determined before widespread primary application can be recommended.

With the global epidemic in diabetes, it is necessary for there to be trials with long-term follow-up in patients with diabetes, in whom the treatment is more complex.[39] Patients with predominantly neuropathic ulceration as opposed to ischemic ulceration will heal with good foot care irrespective of whether they are "revascularized." The TransAtlantic Inter-Society Consensus II guidelines for the management of PAD identify a transcutaneous partial pressure of oxygen of <30 mm Hg for diagnosis of a critically ischemic limb. The International Working Group on the Diabetic Foot guidelines state that wound healing is likely if the transcutaneous partial pressure of oxygen is >50 mm Hg. Unfortunately, very few studies including patients with diabetes and classifying patients with tissue loss reported physiologic data either before or after intervention. It is therefore difficult to judge what proportion of these patients with diabetes had true Rutherford-Baker category 5 or 6 ischemia as opposed to neuropathic ulcers with adequate tissue perfusion. Future trials of drug-eluting technology should report in detail toe pressures, transcutaneous partial pressure of oxygen, and ulcer grading both before and after intervention in patients with diabetes. Indeed, given the predicted magnitude of the problem, it would be prudent to undertake some trials exclusively in diabetic patients with tissue loss and proven critical ischemia.

On the basis of literature review, the U.K. National Institute for Health and Clinical Excellence guidelines for lower limb PAD diagnosis and management have stated that this technology should not normally or routinely be used outside a trial situation. The results of our review, which includes nine additional studies with controls, agree with this conclusion.

There was wide variation in the duration of dual antiplatelet therapy used by the included studies. This is a reflection of the lack of consensus by vascular specialists. In coronary disease, current guidelines recommend 6 to 12 months of dual antiplatelet therapy when DESs are used.[40]

Only 15% of the stented surface in DESs is covered by struts, which limits effective local drug delivery and leads to incomplete endothelialization. To overcome this issue, DEBs coated with antiproliferative pharmaceuticals were introduced.[41,42] The duration of inhibition of cell proliferation far exceeds the time during which the cells are actually exposed to the drug. The cost-effectiveness of DEBs is also under intense scrutiny, as they are designed for single-site inflation only; some long lesions may require multiple inflations, requiring multiple DEBs or additional stenting, dramatically increasing cost of the procedure. There is no consensus as to how some of these devices should be used. Formal cost-effectiveness analysis of DEB and DES use has not been reported.

This systematic overview of best evidence has several limitations. Differences in the drug type and dosage add complexity to the interpretation of outcomes of studies using drug-eluting technology. Because of the relatively small number of studies, we were unable to undertake a meaningful subgroup analysis of the influence of different drug coatings on outcome. There was a wide variation in reporting of patient characteristics and in definitions of outcome. These factors limited the type of meta-analysis that could be performed. Therefore, the importance of using common standards to report results of treatment for PAD and, especially, for endovascular treatment of infrainguinal lesions to facilitate future analyses must be stressed.[43,44] Future trials should separate patients with claudication and critical ischemia. In critically ischemic patients, detailed assessment of physiologic parameters is required. Patients with diabetes should be analyzed in detail as a subgroup or be assessed in separate trials. For patients with claudication, the primary outcomes of interest are changes in walking distance and quality of life, which should be assessed formally. For patients with critical ischemia, the primary outcomes of interest are wound healing and amputation-free survival. At present, end points such as TLR are subjective and ill-defined. In future trials, separate prespecified definitions will be required for claudication, CLI, and diabetic foot ulcers if they area included as secondary end points. Trials of drug-eluting technology in claudicants should be restricted to the femoropopliteal segment. In patients with critical ischemia, multilevel disease is the norm. We therefore do not recommend separate suprapopliteal and infrapopliteal studies. At present, trials should focus on comparing stents and balloons separately.

Cost-effectiveness analysis should be incorporated into future trial designs.

CONCLUSIONS

Studies to date suggest that the concept of drug-eluting endovascular technology holds promise. However, data are sparse and have serious limitations, including potential bias secondary to failure of adequate blinding, use of predominantly radiographic outcomes, relatively short follow-up, relatively small numbers of patients with CLI, and poor representation of patients with diabetes. The management of patients with CLI and diabetes is different from that of the general population and arguably more complex. Separate studies should be designed and implemented to elucidate outcomes in this growing group of patients.[40] The cost-effectiveness of this technology has not been adequately addressed in the literature. Further large and therefore adequately powered randomized controlled trials with long-term follow-up, carefully designed methodology, and robust reporting on clinical outcomes are required before this technology can be considered superior to plain old balloon angioplasty.

AUTHOR CONTRIBUTIONS

Conception and design: BO, LC, RH
Analysis and interpretation: BO, LC, AB, IL, MT, RH
Data collection: BO, LC
Writing the article: BO, LC, RH
Critical revision of the article: BO, LC, AB, IL, MT, RH
Final approval of the article: BO, LC, AB, IL, MT, RH

Statistical analysis: BO, LC
Obtained funding: Not applicable
Overall responsibility: RH
LC and BO contributed equally to this article and hold joint co-first authorship/contributorship on this work.

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